REMARKS/ARGUMENTS

Claims 119-123 are pending in this application.

Claim Rejections – 35 U.S.C. §§101 and 112, First Paragraph

Claims 119-123 remain rejected under 35 U.S.C. §101 allegedly "because the claimed invention lacks a credible, specific and substantial asserted utility or a well established utility."

Claims 119-123 remain further rejected under 35 U.S.C. §112, first paragraph, allegedly "since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility, one skilled in the art would not know how to use the claimed invention." (Page 2 of the instant Office Action).

The Examiner maintains that the Applicants' assertion of utility is not substantial based on the teachings of Pennica *et al.*, Haynes *et al.*, Hu *et al.*, and Chen et al. The Examiner adds that there "is a lack of correlation between and among DNA amplification, mRNA, and increased peptide levels." (Page 3 of the instant Office Action).

Arguments

Applicants maintain that the specification, as filed, provides sufficient disclosure to establish a specific, substantial and credible utility for the PRO1153 polypeptide of SEQ ID NO:351 and antibodies to which it binds. Applicants add that based on the teachings within the Goddard declaration that the gene amplification of the DNA encoding PRO1153 is significant and therefore is sufficient to confer patentable utility to the instantly claimed PRO1153 polypeptides and its antibodies.

As discussed previously, it is not a legal requirement to establish a "necessary" correlation between an increase in the copy number of the mRNA and protein expression levels that would correlate to the disease state or that it is "imperative" to find evidence that protein levels can be accurately predicted. As discussed above, the evidentiary standard to be used throughout *ex parte* examination of a patent application is a preponderance of the totality of the evidence under consideration. Accordingly, the question is not, as the Examiner suggests, whether a necessary or even "strong" correlation between an increase in copy number and protein expression levels exists, rather if it is more likely than not that a person of ordinary skill in the

pertinent art would recognize such a positive correlation. Applicants respectfully submit that when the proper evidentiary standard is applied, a correlation must be acknowledged.

Applicants maintain, for the reasons provided in the previously filed Responses that Pennica *et al.,* Hu *et al.* and Haynes *et al.* do not show that a lack of correlation between gene (DNA) amplification and elevated mRNA levels, in general, exists. Applicants' arguments presented in the previously filed Response of October 27, 2005 and in the Preliminary Amendment of June 30, 2006 are hereby incorporated by reference in their entirety.

Applicants further submit that Example 170 explicitly states that the PRO1153 DNA is significantly overexpressed in lung tumors as compared to the normal control. Therefore, Applicants asserted that one skilled in the art would more likely than not know that the corresponding PRO115 protein is also "most likely" increased in these lung tumors. To support this result, Applicants presented the Declarations of Dr. Polakis. Applicants also asserted that according to the Utility Examination Guidelines, Office personnel must treat as true a statement of fact made by an Applicant in relation to an asserted utility, unless countervailing evidence can be provided that shows that one of ordinary skill in the art wuld have a legitimate basis to doubt the credibility of such a statement.

Alberts and Lewin

While acknowledging that the teaching of Alberts and Lewin supports that the initiation of transcription is the most common point for a cell to regulate the gene expression, the Examiner asserts that the initiation of transcription is not the only means of regulating gene expression according to the teaching of Alberts. (Page 6 of the instant Office Action).

Applicants respectfully disagree and submit that the utility standard is not **absolute certainty**. Rather, to overcome the presumption of truth that an assertion of utility by an applicant enjoys, the PTO must establish that it is **more likely than not** that one of ordinary skill in the art would doubt the truth of the statement of utility. Therefore, Applicants **do not need** to establish that the transcription initiation is **the only means** of regulating gene expression in order to meet the utility standard. Instead, as long as it is the most common point of regulation, as admitted by the Examiner, it would be more likely than not that a change of the transcription

level of a gene gives rise to a change in translation level of a gene. Thus, the utility standard is met.

Meric *et al*

With respect to Applicants' arguments on Meric *et al.*, the Examiner asserts that Meric teaches that the gene expression is quite complicated, and is also regulated at the level of mRNA stability, mRNA translation, and protein stability. (Pages 6 of the instant Office Action).

Applicants emphasize that it is not a legal requirement to establish an absolute correlation between an increase in the mRNA level and protein expression levels that would correlate to the disease state nor is it imperative to find evidence that protein levels can be accurately predicted. Therefore, the Examiner has misinterpreted the teaching of Meric and applied improperly high legal standard.

Applicants respectfully submit that Meric simply summarizes the translation regulation of cancer cells. Meric indicates that translation initiation is regulated in response to nutrient availability and mitogenic stimulation and is coupled with cell cycle progression and cell growth. Meric further discusses that alteration in translation control occur in cancer. For example, variant mRNA sequences can alter the translational efficiency of individual mRNA molecule. (see Abstract). Meric further teaches that the changes of the translational efficiency of a mRNA transcript depend on the mutation of a specific mRNA sequence. (Page 973, column 2 to page 974, column 1). Meric never suggest that the translation of a cancer gene is suppressed in cancer in general, and therefore, an increased mRNA levels will not yield an increased protein levels. To the contrary, Meric teaches that the translation efficiency of a number of cancer genes is enhanced in cancer cells compared to its normal counterpart. For instance, in patient with multiple myeloma, a C-T mutation in the c-myc IRES was identified and found to cause an enhanced initiation of translation. (Page 974, column 1). Therefore, the level of proteins encoded by these genes increases in cancer cells at an even higher magnitude than the mRNA level. As absolute accurate prediction of the protein level based on the mRNA level should not be required, the Examiner has failed to establish a *prima facie* showing of lack of utility in this instance.

Orntoft *et al.*

The Examiner maintains that the Orntoft *et al.*, reference is not persuasive because Specification's disclosure are not characterized on the basis of those in the Orntoft publication. (Page 7 of the instant Office Action).

The Orntoft reference was submitted by the Applicants to show that there was a gene dosage effect and teaches that "in general (18 of 23 cases) chromosomal areas with more than 2-fold gain of DNA showed a corresponding increase in mRNA transcripts." (See column 1, Abstract). Based on this reference and on several other references, Applicants have submitted that it is generally well-understood in the art that DNA copy number influences gene expression. For example, Orntoft *et al.* studied transcript levels of 5600 genes in malignant bladder cancers which were linked to a gain/loss of chromosomal material using an array-based method.

Applicants submit that the DNA encoding PRO1153 would have utility even if it were shown not to be in a gene cluster, because the instant specification has already determined that the PRO1153 DNA is amplified significantly compared to its control. Applicants have provided an expert Declaration (the Goddard Declaration) to support the significance of the values obtained in the gene amplification assay for PRO1153 DNA. Therefore, a utility rejection based on the premise that PRO1153 DNA may not be within an amplified cluster is not appropriate according to the utility standards.

Chen *et al.*

The Examiner cites Chen *et al.*, as comparing mRNA and protein expression for a cohort of genes in the same lung adenocarcinomas. (Page 7 of the instant Office Action).

The manner in which the Chen data was averaged and analyzed is a vastly different manner from that of the instant specification. For example, Chen *et al.* studied expression levels across a set of samples which included a large number of tumor samples (76) and a much smaller group of normal samples (9). The authors determined the global relationship between mRNA and corresponding protein expression using the average expression values for all 85 lung tissue samples. The authors chose an arbitrary threshold of 0.115 for the correlation to be considered significant. This resulted in negative normalized protein values in some cases and the authors concluded that it is not possible to predict overall protein expression based on **average mRNA**

abundance. Applicants remind the Examiner that the utility standard does not require accurate prediction of protein values; only that in a majority of the proteins studied, it is more likely than not that protein levels increased when mRNA levels increased. A review of the correlation coefficient data presented in the Chen *et al.* paper indicates that, in fact, Chen teaches that 'it is more likely than not' that increased mRNA expression correlates well with increased protein expression. For instance, a review of Table 1, which lists 66 genes [the paper incorrectly states there are 69 genes listed] for which only one protein isoform is expressed, shows that 40 genes out of 66 had a positive correlation between mRNA expression and protein expression. This clearly meets the test of "more likely than not." Similarly, in Table II , 30 genes with multiple isoforms [again the paper incorrectly states there are 29] were presented. In this case, for 22 genes out of 30, at least one isoform showed a positive correlation between mRNA expression and protein expression. Furthermore, 12 genes out of 29 showed a strong positive correlation [as determined by the authors] for at least one isoform. **No genes showed a significant negative correlation**. It is not surprising that not all isoforms are positively correlated with mRNA expression. Thus, Table II also provides that it is more likely than not that protein levels will correlate with mRNA expression levels.

Futcher *et al.*

With respect to Futcher *et al*, the Examiner asserts that "even Futcher *et al.* acknowledges that 'Gygi *et al.* feel that mRNA abundance is a poor predictor of protein abundance.'" (Page 8 of the instant Office Action).

Applicants respectfully point out that, on the contrary, Gygi *et al.* never indicate that the correlation between mRNA and protein levels does not exist. Gygi *et al.* only state that the correlation may not be sufficient to **accurately** predict the protein level from the level of the corresponding mRNA transcript. (See page 1270, Abstract). Contrary to the Examiner's statement, the Gygi data indicate **a general trend** of correlation between protein [expression] and transcript levels. (Emphasis added). For example, as shown in Figure 5, the mRNA abundance of **250-300** copies/cell correlates with the protein abundance of **500-1000** x 10^3 copies/cell. The mRNA abundance of **100-200** copies/cell correlates with the protein abundance of **250-500** x 10^3 copies/cell. (Emphasis added). Therefore, high levels of mRNA **generally**

correlate with high levels of proteins. In fact, most data points in Figure 5 did not deviate or scatter away from the general trend of correlation. Thus, the Gygi data meets the "more likely than not standard" and shows that a positive correlation exists between mRNA and protein.

Gygi *et al.* may teach that protein levels cannot be "predicted" from mRNA levels in the sense that the exact numerical amounts of protein present in a tissue cannot be determined based upon mRNA levels. Applicants respectfully submit that the PTO's emphasis on the need to "accurately predict" protein levels based on mRNA levels misses the point. The asserted utility for the claimed polypeptides is in the diagnosis of cancer. What is relevant to use as a cancer diagnostic is relative levels of gene or protein expression, not absolute values, that is, that the gene or protein is differentially expressed in tumors as compared to normal tissues. Applicants need only show that there is a correlation between mRNA and protein levels, such that mRNA overexpression generally predict protein overexpression. A showing that mRNA levels can be used to "accurately predict" the precise levels of protein expression is not required.

Moreover, Futcher *et al.* point out that the "different conclusions" of Gygi *et al.* are also partly due to different methods of statistical analysis, and to real differences in data. Futcher *et al.* note that Gygi *et al.* used the Pearson product-moment correlation coefficient (r_p) and point out that "a calculation of r_p is inappropriate" because the mRNA and protein abundances are not normally distributed. (Page 7367, col. 1). In contrast, Futcher *et al.* used two different statistical approaches to determining the correlation between mRNA and protein abundances. First, they used the Spearman rank correlation coefficient (r_s), an nonparametric statistic that does not require the data to be normally distributed. Using the r_s, the authors found that mRNA abundance was well correlated with protein abundance ($r_s = 0.74$). Applying this statistical approach to the data of Gygi *et al.* **also** resulted in a good correlation ($r_s = 0.59$), although the correlation was not quite as strong as for the Futcher *et al.* data. In a second approach, Futcher *et al.* transformed the mRNA and protein data to forms where they were normally distributed, in order to allow calculation of an r_p. Two types of transformation (Box-Cox and logarithmic) were used, and **both** resulted in good correlations between mRNA and protein abundance for Futcher *et al.*'s data.

Futcher *et al.* also note that the two studies used different methods of measuring protein abundance. Gygi *et al.* cut spots out of each gel and measured the radiation in each spot by

scintillation counting, whereas Futcher *et al.* used phosphorimaging of intact gels coupled to image analysis. Futcher *et al.* point out that Gygi *et al.* may have systematically overestimated the amount of the lowest-abundance proteins, because of the difficulty in accurately cutting out very small spots from the gel, and because of difficulties in background subtraction for small, weak spots.

In addition, Futcher *et al.* note that they used both SAGE data and RNA hybridization data to determine mRNA abundances, which is most helpful to accurately measure the least abundant mRNAs. As a result, while the Futcher data set "maintains a good correlation between mRNA and protein abundance even at low protein abundance" (page 7367, col. 2), the Gygi data shows a strong correlation for the most abundant proteins, but a poor correlation for the least abundant proteins in their data set. Futcher *et al.* conclude that "**the poor correlation of protein to mRNA for the nonabundant proteins of Gygi *et al.* may reflect difficulty in accurately measuring these nonabundant proteins and mRNAs, rather than indicating a truly poor correlation *in vivo.***" (Page 7367, col. 2; Emphasis added). Thus, while these lowest abundant proteins do show a poor correlation, this is almost certainly due to the less accurate methods used to measure the abundance of these proteins, and **not** to any actual lack of correlation.

Polakis Declaration

Regarding the Polakis II Declaration, the Examiner alleges that " the Declaration does not provide data such that the Examiner can independently draw conclusions." (Page 10 of the instant Office Action).

Dr. Polakis' statement that "an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell" is based on factual, experimental findings, clearly set forth in the Declaration. Accordingly, the Declaration is not merely conclusive, and the fact-based conclusions of Dr. Polakis would be considered reasonable and accurate by one skilled in the art. Further, the Examiner has not presented any convincing evidence to indicate that one of ordinary skill in the art would doubt the validity of PRO1153 proteins have utility in the diagnosis of cancer.

The Examiner adds that Dr. Polakis is employed by the assignee. (Page 14 of the instant Office Action).

Applicants note that the sworn Declaration of Dr. Polakis is sufficient to support Applicants' position that the gene amplification influences gene expression at the mRNA and protein levels.

Taken together, despite some teachings in the art of certain genes that do not fit within this paradigm which are exceptions rather than the rule, in the vast majority of amplified genes, the combined teachings in the art as exemplified by Orntoft *et al.* and other references discussed and submitted in this case, as well as the Polakis Declaration, overwhelmingly teach that gene amplification influences gene expression at the mRNA and protein levels. Thus, one of skill in the art would reasonably expect, in this instance, based on the amplification data for the PRO1153 gene, that the PRO1153 protein is concomitantly overexpressed. Thus, Applicants submit that the PRO1153 proteins have utility in the diagnosis of cancer and based on such a utility, one of skill in the art would know exactly how to use these molecules.

In conclusion, Applicants have demonstrated a credible, specific and substantial asserted utility for the PRO1153 polypeptides and the antibodies that bind to it, for example, in detecting over-expression or absence of expression of PRO1153. In fact, the art also indicates that, if a gene is amplified in cancer, it is **more likely than not** that the encoded protein will also be expressed at an elevated level. Based on these discussions, one skilled in the art, at the time the application was filed, would know how to use the claimed polypeptides and the antibodies that bind to it. Hence, these data clearly support a role of PRO1153 as a lung tumor marker.

Therefore, Applicants request that the Examiner reconsider this rejection and maintain that they have demonstrated utility for the PRO1153 polypeptide and antibodies thereof as diagnostic markers for human lung tumors. Accordingly, the present 35 U.S.C. §101 and §112, first paragraph, utility rejections should be withdrawn.

CONCLUSION

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** (referencing Attorney's Docket No. **39780-2730 P1C32**).

Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: July 11, 2007

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SV 2286847 v1
7/11/07 9:54 AM (39780.2730)